

AMENDMENT TO THE CLAIMS:

This listing of Claims will replace all prior versions of Claims in the application. Changes to the claims are indicated by strikethrough or double-bracketing for deleted matter and by underlining for added matter.

Listing of Claims:

1-88. (Canceled).

89. (Currently Amended) An in vitro composition of cultured cells comprising modified cells and unmodified cells of an inbred strain of an animal, and/or or the progenies thereof or both, said modified cells each comprising at least one modification sequence, said composition being produced by a method comprising introducing a targeting DNA construct into a plurality of unmodified cells of an inbred strain of animal in vitro, wherein said targeting DNA construct comprises a targeting DNA sequence that is capable of homologous recombination with a non-selectable target DNA sequence in the genome of said plurality of unmodified cells, and wherein said targeting DNA sequence comprises: (i) said at least one modification sequence, and (ii) flanking sequences that are derived from said inbred strain of animal.

90. (Currently Amended) The composition of claim 89, said method further comprises incubating said modified cells and said unmodified cells, and/or or the progenies thereof or both, under conditions where said targeting DNA sequence undergoes homologous recombination with said target DNA sequence in the genome of said modified cells.

91. (Previously Presented) The composition of claim 90, wherein said targeting DNA construct is produced in a prokaryotic cell.

92. (Previously Presented) The composition of claim 91, wherein said prokaryote is *E. coli*.

93. (Previously Presented) The composition of claim 90 wherein 5% to 25% of said plurality of unmodified cells have taken up said targeting DNA construct and undergone homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence.

94. (Previously Presented) The composition of claim 90 wherein 10% to 90% of said modified cells have undergone homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence.

95. (Previously Presented) The composition of claim 90 wherein 30% to 50% of said modified cells have undergone homologous recombination between said target DNA sequence in the genome and said targeting DNA sequence.

96. (Previously Presented) The composition of claim 89 or 90, wherein said inbred strain of animal is a non-murine animal, a non-human animal, a mammal, or a vertebrate.

97. (Previously Presented) The composition of claim 89 or 90, wherein said inbred strain of animal is a mouse.

98. (Previously Presented) The composition of claim 89 or 90, wherein said modified cells are stem cells, germ cells, or somatic cells.

99. (Withdrawn) The composition of claim 89 or 90, wherein said modified animal cell is a hematopoietic cell, a T-lymphocyte, an epithelial cell, an endothelial cell, an adrenal medulla cell, a keratinocyte, a fibroblast, an osteoblasts, an osteoclasts, a neuron, a ganglion cell, a retinal cell, a liver cell, a myoblast cell, or a cell of the Islets of Langerhans.

100. (Previously Presented) The composition of claim 89 or 90, wherein said modified cells are embryonic stem cells.

101. (Previously Presented) The composition of claim 89 or 90, wherein said target DNA sequence comprises a coding region, a promoter, an enhancer, a terminator, an intron, or an inter-genic region.

102. (Previously Presented) The composition of claim 89 or 90, wherein each of said flanking sequences is at least about 75, 100, 150, 200, 300, 500, 1,000, 2,500, 8,000 or 15,000 base pairs.

103. (Previously Presented) The composition of claim 89 or 90, wherein each of said flanking sequences is at least 97%, 99%, 99.5%, 99.6%, or 99.9% identical to said target DNA sequence.

104. (Previously Presented) The composition of claim 89 or 90, wherein said target DNA sequence and each of said flanking sequences comprises at least about 75, 150, or 500 base pairs in length that are 100% identical.

105. (Previously Presented) The composition of claim 89 or 90, wherein said targeting DNA sequence is derived from cells of the same individual animal or a sibling thereof, as cells comprising said target DNA sequence.

106. (Previously Presented) The composition of claim 89 or 90, wherein said targeting DNA construct comprises a gene that is a selectable marker, an antibiotic resistance gene, a gene conferring the ability to grow on selected substrates, or a gene encoding proteins that produce detectable signals.

107. (Previously Presented) The composition of claim 106, wherein said gene is positioned in an intron in the targeting DNA.

108. (Previously Presented) The composition of claim 106 wherein said gene comprises a transcriptional start signal, a translational start signal, and/or a termination signal.

109. (Previously Presented) The composition of claim 106 wherein said gene is a neomycin resistance gene, a hygromycin resistance gene, a thymidine kinase gene, a hypoxanthine phosphoribosyl transferase gene, or a guanine/xanthine phosphoribosyl transferase gene.

110. (Previously Presented) The composition of claim 108, wherein said transcriptional start signal comprises a metallothionein promoter, a thymidine kinase promoter, a beta-actin promoter, an immunoglobulin promoter, a SV40 promoter, or a human cytomegalovirus promoter.

111. (Previously Presented) The composition of claim 89 or 90, wherein said modification sequence comprises a gene that is a selectable marker, an antibiotic resistance gene, a gene conferring the ability to grow on selected substrates, or a gene encoding proteins that produce detectable signals.

112. (Previously Presented) The composition of claim 89, wherein said introducing step comprises the use of microinjection, electroporation, transfection, calcium phosphate precipitation, liposomes, viral capsids, protoplast fusion, or ballistic penetration.

113. (Previously Presented) The composition of claim 90, wherein said method further comprises selecting said modified cells and progenies thereof.

114. (Previously Presented) The composition of claim 90, wherein said target DNA sequence in said modified cells is modified by an insertion, a deletion, a substitution, or a combination thereof.

115. (Previously Presented) The composition of claim 89 or 90, wherein said at least one modification sequence is a sequence that is not present in the genome of said inbred strain of animal.

116. (Previously Presented) The composition of claim 114, wherein said deletion comprises a deletion of at least one exon, at least one intron, at least a non-coding region, or a combination thereof.

117. (Previously Presented) The composition of claim 90, wherein said at least one modification sequence disrupts or enhances expression of a coding sequence in said target DNA sequence.

118. (Previously Presented) The composition of claim 90, wherein said homologous recombination comprises a single crossover, a double crossover, or a gene conversion.

119. (Previously Presented) The composition of claim 90, wherein an allele of a gene in said target DNA has been modified.

120. (Previously Presented) The composition of claim 119, wherein the other allele of said gene has been modified.

121. (Previously Presented) The composition of claim 89 or 90, wherein said inbred strain of animal is 129 strain of mouse or BALB/c strain of mouse.

122. (Previously Presented) The composition of claim 89 or 90, wherein said plurality of unmodified cells are cells of a substrain of said inbred strain of animal.

123. (Previously Presented) The composition of claim 89 or 90, wherein said targeting DNA sequence is from a substrain of said inbred strain of animal.

124. (Previously Presented) The composition of claim 89 or 90, wherein said plurality of unmodified cells are derived from a first substrain of said inbred strain of animal and said targeting DNA sequence is from a second substrain of said inbred strain of animal.

125. (Previously Presented) The composition of claim 124 wherein said first substrain and said second substrain are the same substrain.

126. (Previously Presented) The composition of claim 89 or 90, wherein said at least one modification sequence comprises a nucleic acid that encodes a polypeptide and wherein said modified cells produce said polypeptide.

127. (Previously Presented) The composition of claim 90, wherein said at least one modification sequence corrects a defective gene in said target DNA.